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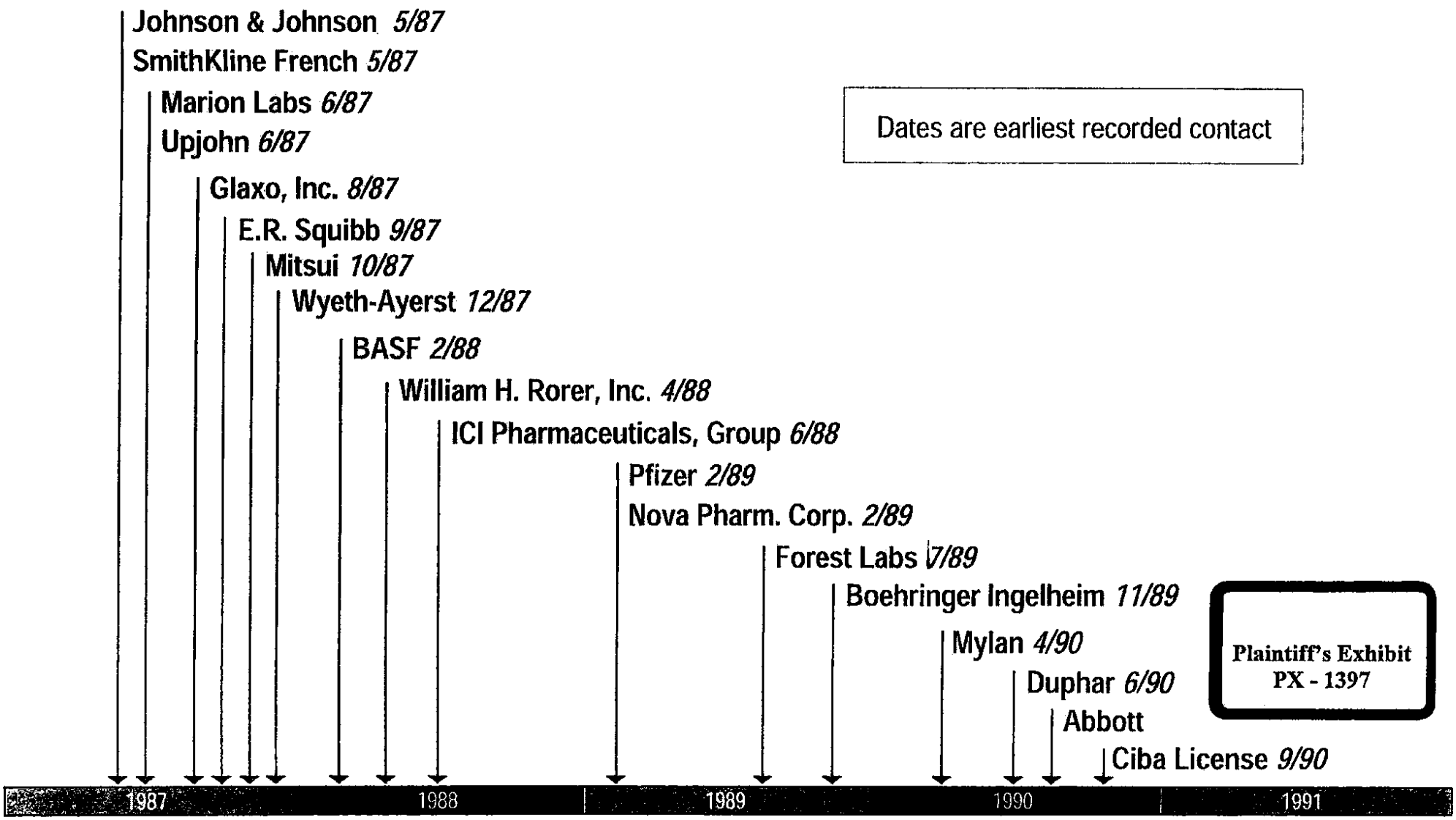
EXHIBIT 56

Skepticism about Galantamine

Dr. Davis' Efforts to Market Her Invention, 1987 – 1990



Dates are earliest recorded contact

Plaintiff's Exhibit
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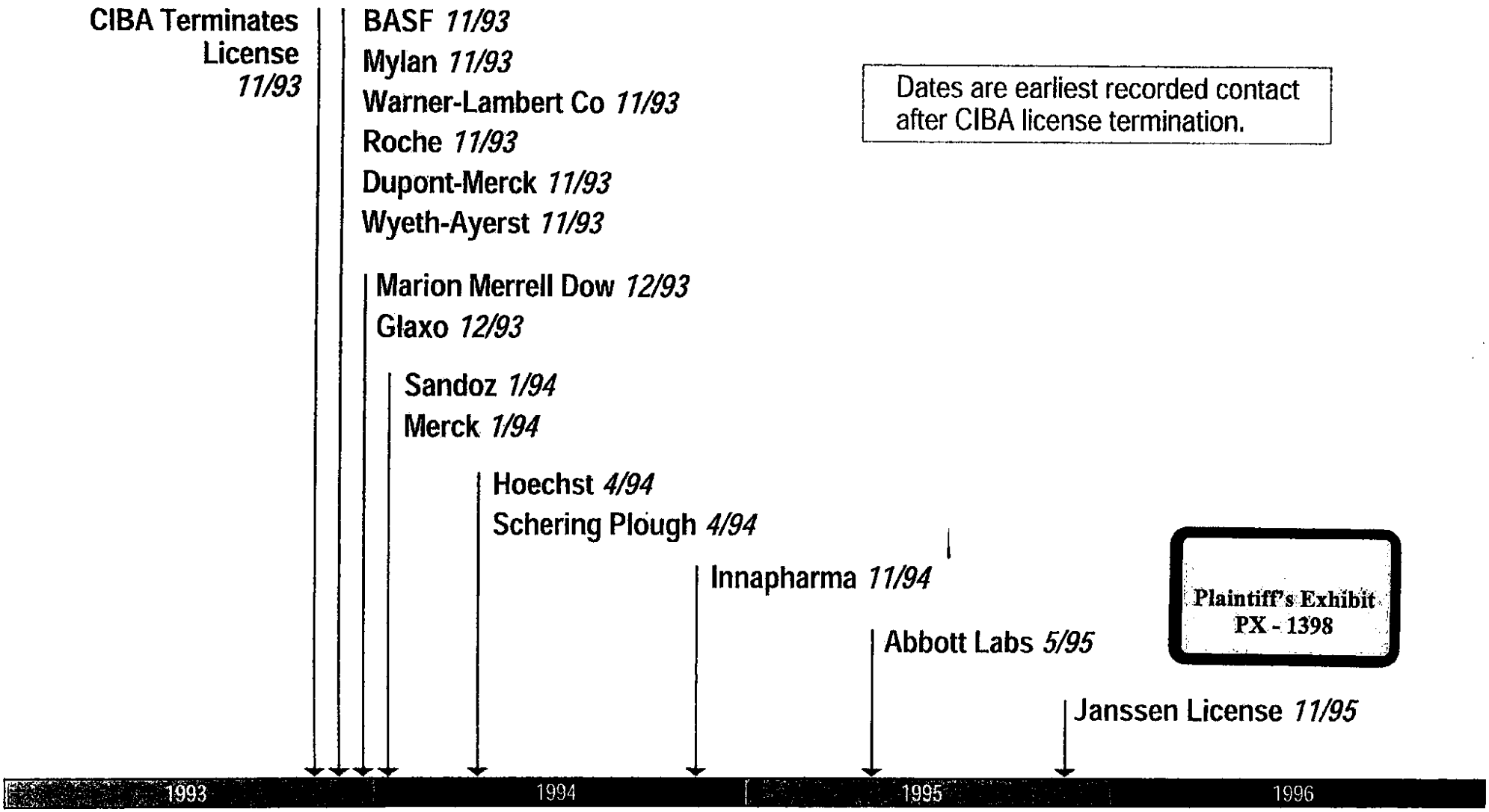
Shire Licenses Foreign Counterparts *1990*

Dates and company names derived from: PX 493, 565, 1067, 578,595, 469, 523, 830, 561, 490, 545, 544, 481, 456, 532, 576, 448, 305 and DX 114

EXHIBIT 57

Skepticism about Galantamine

Dr. Davis' Efforts to Market Her Invention, 1993 – 1995



Dates are earliest recorded contact after CIBA license termination.

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EXHIBIT 58

The Cholinergic Synapse

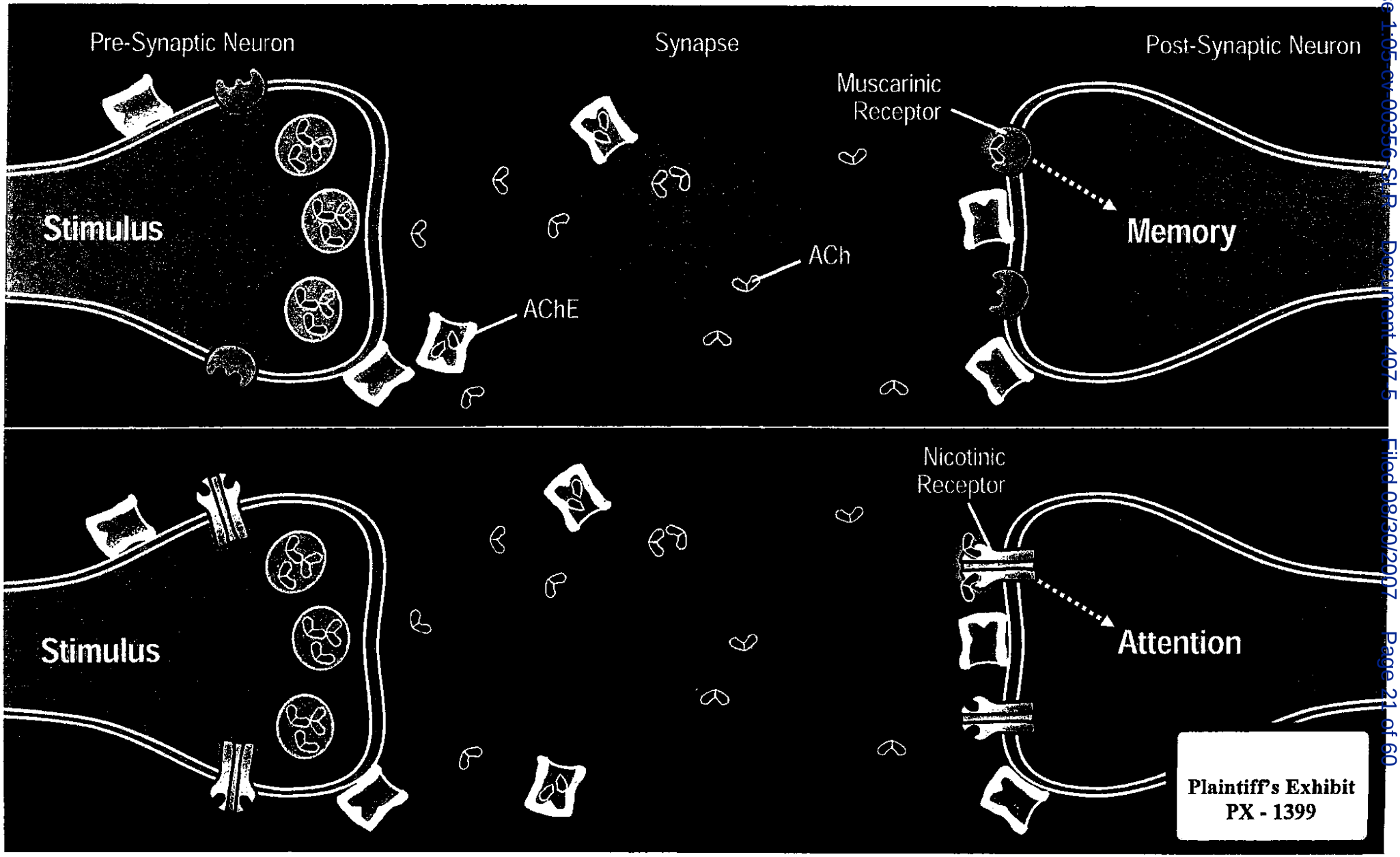

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EXHIBIT 59

The Neuroendocrine Window

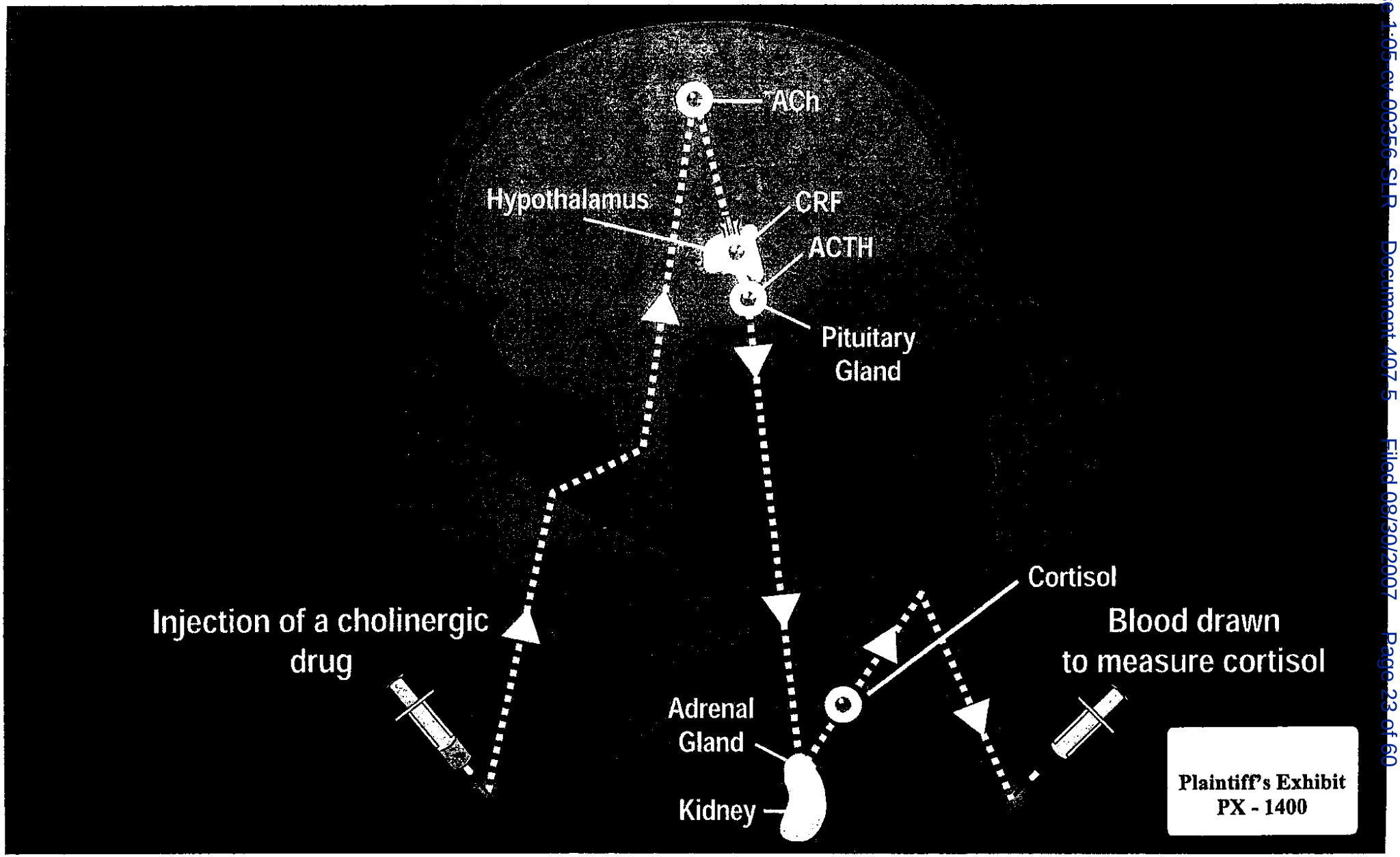
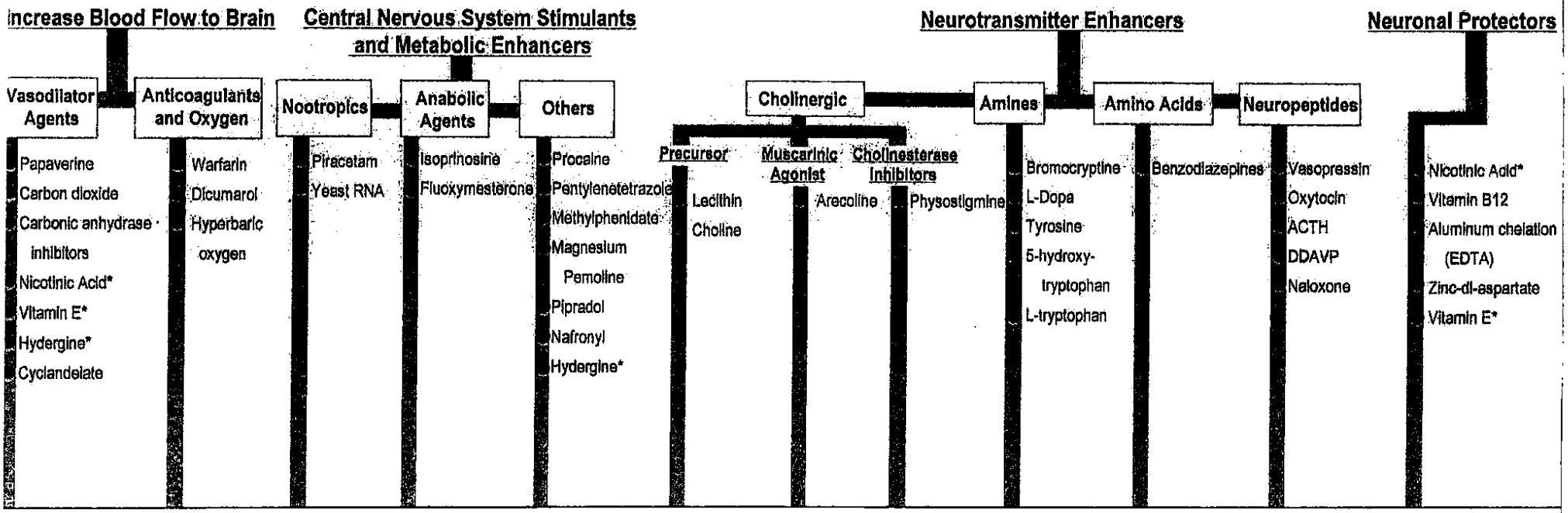


EXHIBIT 60

The Search for An Alzheimer's Treatment Pre-1986



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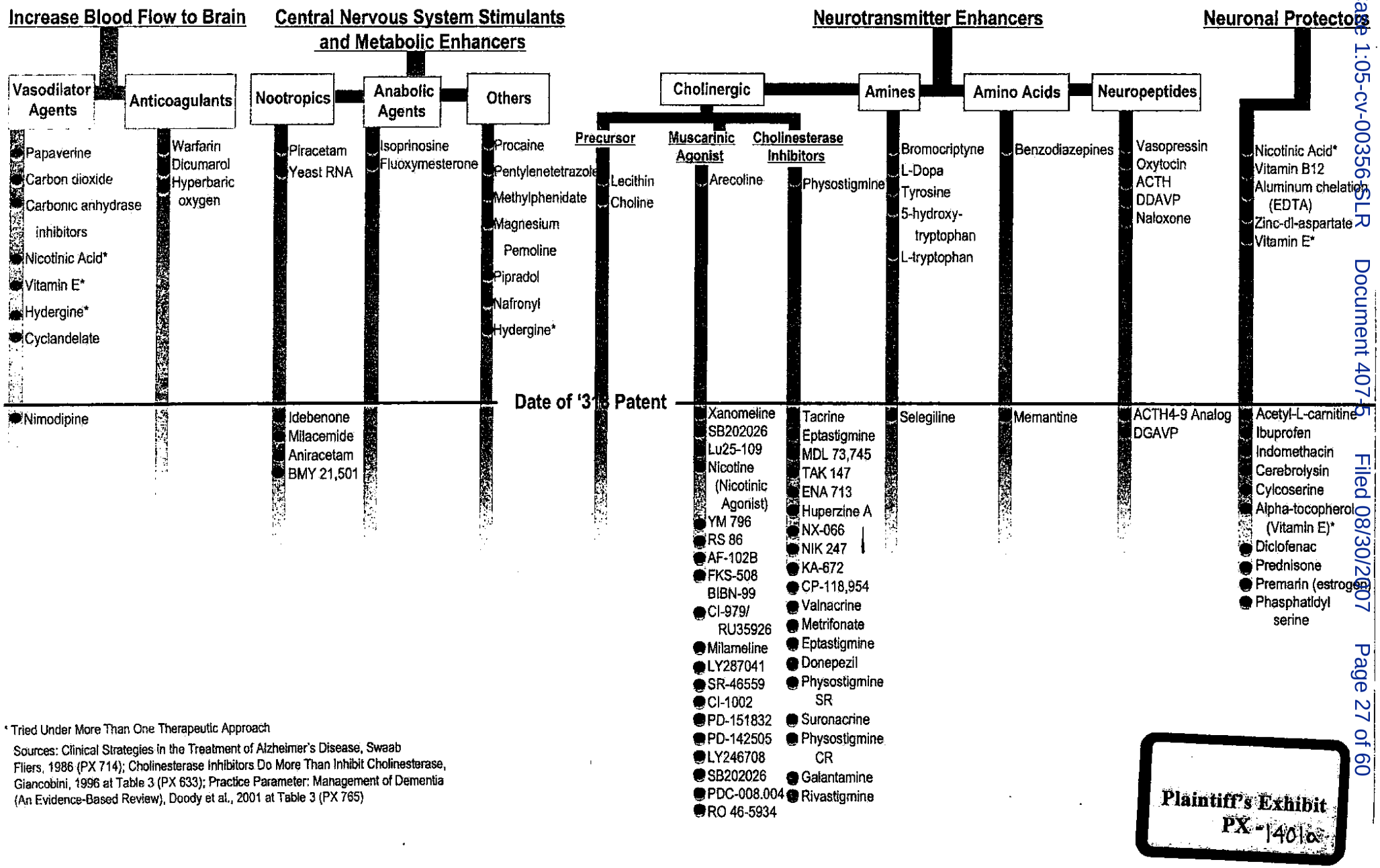
Tried Under More Than One Therapeutic Approach

Sources: Clinical Strategies in the Treatment of Alzheimer's Disease, Swaab & Fliers, 1986 (PX 714)

EXHIBIT 61

The Search for An Alzheimer's Treatment Up to 2001



* Tried Under More Than One Therapeutic Approach

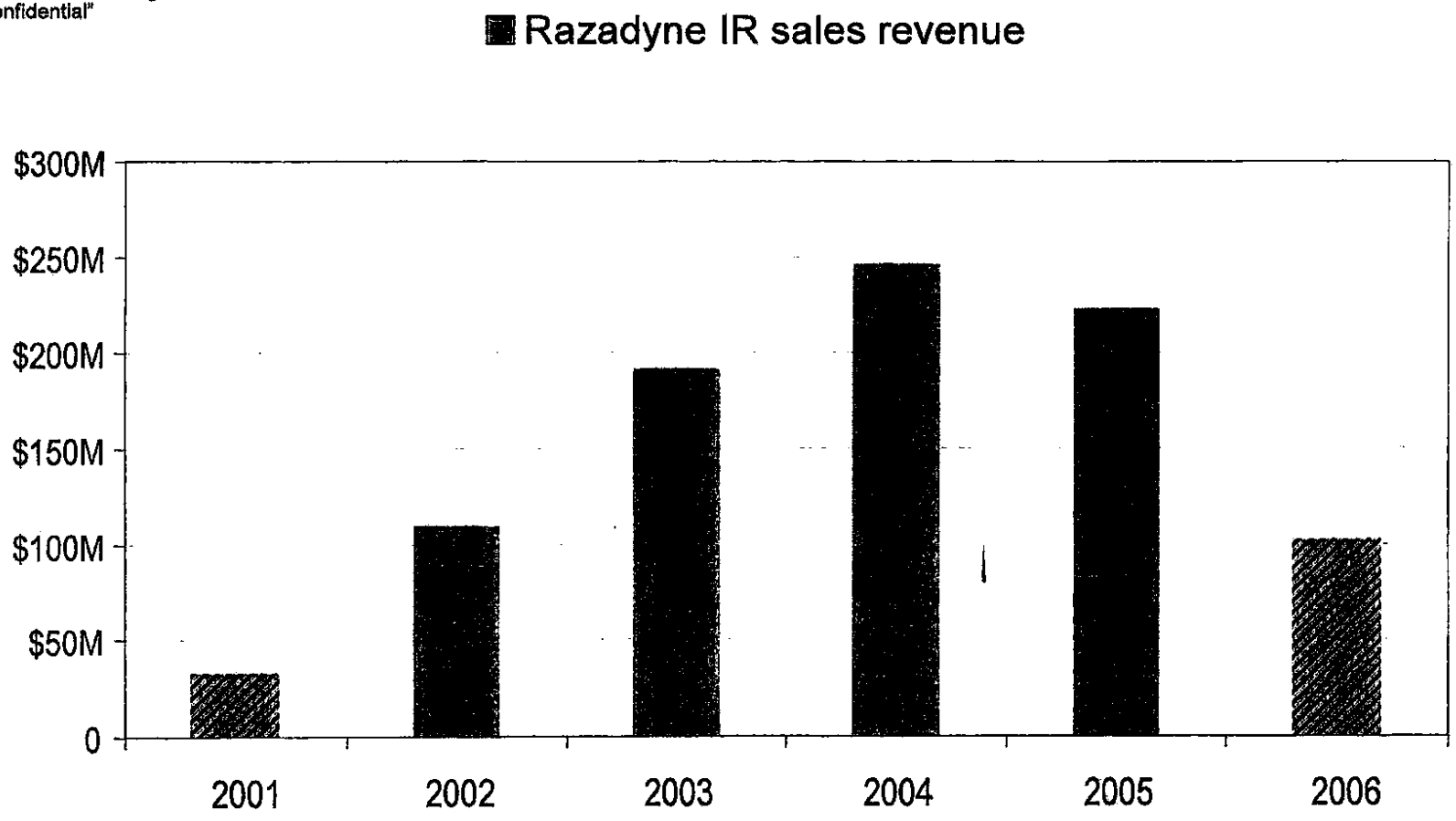
Sources: Clinical Strategies in the Treatment of Alzheimer's Disease, Swaab Fliers, 1986 (PX 714); Cholinesterase Inhibitors Do More Than Inhibit Cholinesterase, Giancobini, 1996 at Table 3 (PX 633); Practice Parameter: Management of Dementia (An Evidence-Based Review), Doody et al., 2001 at Table 3 (PX 765)

Plaintiff's Exhibit PX-1401a

EXHIBIT 62

Razadyne IR has sold over $912.6 million

Subject to Protective Order
Contains Information Designated
"Highly Confidential"



Partial year data: Razadyne IR was launched in May of 2001; 2006 data available only through August 2006

Source: PX 297a, 311
Note: Not adjusted for inflation

Plaintiff's Exhibit
PX-1402

EXHIBIT 63

p.3

Neurology and Neurosurgery

vol 33

Excerpta Medica Sect. 8 Neurology and Neurosurgery
Vol 33, 1975

...ns, which would explain the said
...s product of a connective tissue
...ect at the dura mater level, is
...ferential diagnosis from
...s can only be achieved through

...voked response in two cases of
...phalocele - POTENTIELS EVOQUES
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...nd Buchan G.C. - Oregon Med. Sch.,
... - REVUE NEURO-PSYCHIAT. 1974 46/2

...thors report 2 cases of occipital
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...the paroxysmal electrical discharges
...rant cerebral tissue provoked no
...isions, probably because of the lack
...between the encephalocele and the
...brain.

...lo radial dysplasia. Report of a
...P.S., Singh H., Lal J.C. and Gupta
...Med. Coll. Hosp. Rohtak -
...1973 40/309 (365-367)
...with bilateral absence of the
...teral radial aplasia, bilateral talipes
...incomplete descent of testes, internal
...and ventricular septal defect
...dial dysplasia) is reported and a
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NEUROLOGY OF MENTAL DISEASE

...role of cerebral aminoacids in
...xic effects of DDT in mice - Kar
...ia M.A. - Industr. Toxicol. Res. Cent.,
...l Palace, Lucknow - EUR.J.PHARMACOL.
...1 (28-32)
...ndotoxic effects (hyperexcitability,
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...n of p,p' DDT (1,1,1 tricnloro 2,2 bis(4'
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...s of GABA glycine and taurine in
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...s of aspartic acid, a alanine,
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...the same dose of o,p' DDT (1,1,1
...chlorophenyl)2(4' chlorophenyl
...to produce any of these symptoms
...alter the concentration of amino
...brain of mice. The results suggest
...mino acids in the cerebral
...may possibly be involved in the
...ffects observed after the
...of p,p' DDT.

2357. The etiopathogenesis and morphology of spontaneous and experimentally produced neurofibrillary degeneration - Onol B. - Fac. Med., Hacettepe Univ., Ankara - HACETTEPE BULL.MEDICINE. 1973 6/2-3 (68-82)

The aluminum salts (tri virelon, quadro virelon, tetanus toxoid) that were used as antigen adsorbents in vaccine production, were given to rabbits through the cisterna magna to ascertain their effects on the central nervous system. The tetanus toxoid which contained aluminum phosphate produced ataxia, hypersensitivity, and convulsions, namely, status epilepticus. Tri virelon and quadro virelon which contain aluminum hydroxide produced no pathological side effects, either clinically or morphologically. The neurofibrillary changes produced experimentally and the spontaneous changes that were seen in presenile and senile dementia, inclusion encephalitis and amaurotic idiocy, are described and the possible etiopathogenesis of the lesions are discussed.

2358. Medical management of dementia - Bhasker P.A. - Dept. Neurol., Inst. Neurol., Government Gen. Hosp., Madras - ANTISEPTIC 1974 71/1 (45-47)

Dementia is neither a disease per se nor a single symptom. It may be considered to be a clinical manifestation resulting from complex structural or functional changes in the most sophisticated mechanisms of the brain. The prognosis becomes excellent when the correctable cause is diagnosed early and found to be a metabolic or endocrine deficit (as in pellagra, B_{12} deficiency or myxedema). The dementing process can be arrested or reversed to a minor extent in cases of tumors (when removable), infections (like GPI) when they can be successfully arrested, post traumatic dementias, and low pressure hydrocephalus. With regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible. Rewarding experiences are on record of treating Huntington's Chorea patients with Haloperidol, a very useful drug in the control of hyperkinetic dyskinesias. A demented person obviously requires careful supervision and devoted nursing care as he will not be able by himself to attend to his own nutrition and personal cleanliness. He is also likely to be unmindful of any intercurrent illnesses that may occur.

2359. Functional asymmetry of the cerebral hemispheres and local lesions of the brain (Russian) - Dobrokhotova T.A. and Braghina N.N. - n.i. Inst. Psikhiat., Min. Zdravookhr. RSFSR, Moscow - VOPR.PSIKHON. 1974 20/2 (96-103)

Changes in the general mental activity differ as between lesions of the midline and the bilaterally represented structures of the brain. Lesions of the former are accompanied by global shifts of the mind (either intensification or depression), while lesions of the latter lead to more differentiated disturbances of mental activity, the disturbances differing as between the symmetrical regions of the hemispheres. A generalized description of the psychopathologic symptoms of lesions of the left and right

S 8 425

Dementia and galantamine

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Managing Editor
REINDERS FOLMER

Medical Abstracting Service

Excerpta Medica
305 Keizersgracht
Amsterdam
The Netherlands

p6

DX-00074-00004

Tissot A. - Cent. Neuropsych. D'Aphasiol. Clin. Univ. Neurol., Geneve - REV. LARYNGOL. 1973 3/5 (97-117)

Speech therapy can only rarely restore to the aphasic his original speech. One must therefore be satisfied with a level of communication sufficient for reintegration into the family, into society and, more rarely, into professional life. The role of the family is primary. To be effective they must be capable of seeing beyond the drama of the situation by taking an active part in reeducation, and of adopting an encouraging attitude aimed at restoring to the patient maximum autonomy. The physician's detachment and practical advice will best help the family to understand the aphasic and to support him in his efforts. Moreover, the family must be in a position to carry on their efforts after the difficult decision to discontinue treatment. This may occur where it is possible to introduce the patient to a group of aphasics undergoing reeducation. A successful outcome would be a spontaneous reunion of the group in the absence of the physician. This constitutes an important step toward reintegration into society.

905. The possibilities of the use of electronic pocket reckoners in the speech training of aphasics - ÜBER. DIE MÖGLICHKEIT. A LER VERWENDUNG DES ELEKTRONISCHEN TASCHENRECH E S BEIM IN DER SPRACHHEILBEHANDLUNG VON APHAS KERN - Enzich I.F. - Cottage Gasse 45 1/7, Wien - Z. HNO. 1974 12/2 (98-103)

The application of the electronic pocket calculator to speech training of aphasics is discussed.

906. Influence of levodopa on the psychopathologic symptoms in parkinsonian patients - DIE WIRKUNG VON L-DOPA AUF DIE PSYCHOPATHOLOGISCHEN SYMPTOME E I PARKINSON KRANKEN - Ozek M. and Aydogmus K. - Psychiat. Klin., Med. Fak., Istanbul - NÖR. PSIKIYATARS. 1973 10/3-4 (150-160)

L-Dopa was administered to a group of 40 patients with idiopathic Parkinson's syndrome (in 18 cases, 2-4 x 50 mg/week i.v., in the other patients 3 g/day by mouth) and the psychopathologic changes recorded. The L-dopa treatment, which was aimed at the neurologic symptoms, caused, to a varying degree, an improvement in the affective modulation in 3/4 of the patients, and also caused an activation of the intellectual processes and an increase in the vital feelings in all patients. In 4 cases psychic complications developed, such as absent mindedness, internal and motor unrest and disturbed orientation. These could be dealt with by using neuroleptics or tranquilizers.

907. Influence of desciidium on behavior in the aged subject - ACTION DU DESCLIDE M SUR LE COMPORTEMENT DU SUJET AGE - De Sauniere J.L. - ARS MEDICI (Rome) 1974 29/2 (323-331)

The influence of viquidil on the behavior of elderly subjects with cerebrovascular disease was studied in 1,413 patients. 76.4% of the patients showed improvement; 13.4% did not show further deterioration; and in 10.2% the treatment had to be discontinued for some reason. In a group of 170 patients the viquidil treatment was by the administration of a vasodilator, group 50.2% improved. The method of is described.

908. Aspects of cerebrovascular disease - M. - Dept. Neurol., Reg. Neurol. Cent., Hosp., Romford - UPDATE 1974 8/5 (991-

A recent combined centre study in which many factors were studied in stroke, including diet, obesity, diabetes, lipids, emphasised that there were 3 fac which stood well above the rest in imp hypertension, transient ischemic attacks disease. The more that can be done, the combat these at an early stage, the gre likelihood of reducing the incidence of

909. Free word association of adult aph - Timmermans H. and Kumin L. - Easter Treatm. Cent., Baltimore, Md. - PSYCHOTH 34/2 (389-390)

Free associations of 10 aphasic-a matched normal subjects indicated that could identify two types of aphasic syn and that auditory presentation produced mature responses, whereas pictures pro more label responses. Results also demo that normal subjects produced a greater of both paradigmatic and syntagmatic than aphasics.

910. Medical management of dementia - P.A. - Dept. Neurol., Inst. Neurol., Govt. Gen. Hosp., Madras - ANTISEPTIC 1974 7

Dementia is neither a disease nor single symptom. It may be considered clinical manifestation resulting from co structural or functional changes in the sophisticated mechanisms of the brain. prognosis becomes 'excellent' when the cause is diagnosed early and found to metabolic or endocrine deficit (as in pe deficiency or myxedema). The dementi can be arrested or reversed to a mino cases of tumors (when removable), infe GPI) when they can be successfully a traumatic dementias, and low pressure hydrocephalus. With regard to progress dementia, there appears very little to management and no treatment is possi Rewarding experiences are on record Huntington's Chorea patients with Hal very useful drug in the control of hyp dyskinesias. A demented person obvio requires careful supervision and devot care as he will not be able by himself to his own nutrition and personal clean is also likely to be unmindful of any illnesses that may occur.

911. Differential diagnosis of the cereb - DIE DIFFERENTIALDIAGNOSE DES ZEREBRALE Summer K. - Neurol. Univ. Klin., Wien ARTERIOSKLEROTOL. 1974 4/3 (136-145)

It is demonstrated in a rough sch in a short description that it is possi practitioner to differentiate at first exa in the hospital between ischaemic and haemorrhagic stroke in the majority o

Section

EXHIBIT 64

MEDICAL MANAGEMENT OF DEMENTIA*

P. A. BHASKER, M.D., D.M. (NEURO.).
Asst. Prof. of Neurology, Institute of Neurology, Government General Hospital, Madras 3

DEMENTIA is neither a disease *per se* nor a single symptom. It may be considered to be a clinical manifestation resulting from complex structural or functional changes in the most sophisticated mechanisms of the brain. The corrective treatment is usually therefore, one associated with a gloomy outlook, because a dementing process in most cases is a relentlessly progressive one, and very often not amenable even to diagnosis.

On the other hand, this gloomy picture is thoroughly wiped out and a favourable result readily obtained when one of the treatable underlying causes is detected; the prognosis becomes 'excellent' when the correctable cause is diagnosed early and found to be a metabolic or endocrine deficit (as in Pellagra, B_{12} deficiency or Myxœdema). In such cases, the dementia can be cleared up and the patient can have a complete "cure".

On the other hand, the dementing process can be arrested or reversed to a minor extent in some instances, where only a guarded prognosis can be offered. These situations include the cases of tumours (when removable), infections (like GPI) when they can be "successfully" arrested, post-traumatic dementias, and low pressure hydrocephalus.

The irreversible cases belong to the category of dementias where there is a progressive fall-out of neurons and the course of the illness is rapidly downhill. Therefore, the importance of a thorough diagnosis even at the first instance must be realised, because the compartmentalisation into treatable and untreatable dementias has to be made with the utmost care. Moreover it must be emphasised that in certain situations (like Myxœdema) a *late* diagnosis of the underlying cause may lead to irreversibility of the mental status, especially so, in the young developing brains.

With regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible. The problem of who is going to manage the dementing individual arises next. Contrary to the older beliefs that the demented person (who is likely to be insane) has to be necessarily managed by a psychiatrist or an internist, it now appears that the Neurologist is the best person to handle them, and a neuropsychiatrist is the ideal person. The neurologist remains today at the centre of a triangle formed by the psychiatrist, the general physician and the neurosurgeon.

*Summarised from the talk given at the Institute of Neurology. Specially contributed to the 'ANUSKRUTIS'.

The control of convulsions and involuntary movements are separate subjects by themselves. But what must be stressed is the importance of controlling these associated disorders which may sometimes assume greater importance than the dementia itself. For example, in cases of Huntington's chorea where the dementia may be very slowly progressive, the involuntary movements may present the main problem, when adequate control of the choreic movements enables the individual to go back to his work. Rewarding experiences are on record of having treated patients with Huntington's Chorea by giving Haloperidol, a very useful drug in the control of hyperkinetic dyskinesias.

The behavioural problems met with in patients with dementia are profound and so depending upon the nature of the behavioural disturbance, judicious use may be made of drugs, along with psychiatric care. General surgical therapy does not find a significant role in dealing with patients suffering from progressive dementia except when there is an isolated behavioural aberration that can be selectively tackled by Stereotaxy. Even then, any beneficial response is short-lived and soon overtaken by the dementing process.

A demented person obviously requires careful supervision and devoted nursing care as he will not be able by himself to attend to his own nutrition and personal cleanliness; he is also likely to be unmindful of any intercurrent illnesses that may supervene.

The restoration of higher cortical functions is difficult and was once considered to impossible; but it has lately gained importance. Luria and his colleagues have dealt with this problem in great detail. They have suggested measures of improving the higher functions in cases of local brain damage like tumour, head injury, infarct etc, by deinhibitory procedures and re-education of the rest of the brain. Deinhibition refers to the facilitation of acetylcholine activity by giving small daily doses of Cholinesterase inhibitors (Neostigmine, Gallanthamine etc.). Empirical measures, like trying anabolic steroids, vasodilators, nucleic acid preparations, amines and aminoacids are in vogue, but have not been of any great value. The problem of sending a demented individual back to his profession has to be adequately studied by the attending physician before coming to a definite decision. If he happens to hold a position requiring the use of proper judgement, it is better that he is relieved of such a responsible post and assigned a less exacting, general type of work.

The social aspects include adequate counselling in marriage affairs when a demented person or a relative of a demented

person seeks advice. The stigma associated with dementia is equal to that with epilepsy. This fact must be kept in mind by the physician, when confronted with a case of dementia and especially the relatives.

The problem of managing a demented individual in a very real one needing adequate judgement, judicious use of drugs, sympathetic nursing and proper counselling.

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DEATHS INVOLVING PROPOXYPHENE

A STUDY OF 41 CASES OVER A TWO-YEAR PERIOD

Forty-one deaths occurred involving propoxyphene hydrochloride (Darvon) during a two year period. Ten patients died from propoxyphene intoxication alone, while 12 were victims of a propoxyphene alcohol combination, the latter number being identical to the deaths from a combination of barbiturates with alcohol seen during the same period. Five young women died from an ingestion of propoxyphene following an argument. Four patients could be categorized as drug abusers due to historical circumstances. The high levels of propoxyphene suggested habituation in three instances. Physicians should be alerted to the potential deleterious effects of indiscriminate use and abuse of propoxyphene, and should warn their patients not to drink alcoholic beverages when taking propoxyphene. They should use extreme caution when prescribing it to those in the younger age-group.

An impressive factor in this series is the availability of the drug to young people who, after a sudden argument, seem to find ingestion of pills a convenient gesture at attempted self-destruction. There were five cases of teenagers (all girls) in this series (aged 15 to 20 years) whose deaths were caused by propoxyphene intoxication, and in none of these were alcohol, other drugs or narcotics addiction involved. In two instances, the victims were found to be pregnant. Ten of the 22 patients who died from ingestion of propoxyphene alone, or propoxyphene in combination with alcohol, were over 40 years of age. while two of the deaths due to the combination were in patients over 60 years of age.

Concerning the manner of death, 17 of the 41 cases were classified as suicide, with six of these solely from the ingestion of propoxyphene.

Eighteen of the 41 patients received a prescription of propoxyphene from one or more private physicians. Seven of these patients eventually died from ingestion of propoxyphene or propoxyphene with alcohol. In 12 instances, the patient secured a prescription as an outpatient from a clinic. —(Sturner Q. William and Garriott C. James, *J.A.M.A.*, 5-3-1973).

Vol. 71, No. 1 Regd. No. 9, M. 429 JANUARY, 1974

The Antiseptic

A Monthly Journal of Medicine & Surgery

For the use of Registered Medical Practitioners only

Editorial & Publishing Office: 323-24, Thambu Chetty St., Madras-600001

Founded by the late Dr. U. RAMA RAU in 1904 Past Editor late Dr. U. KRISHNA RAU

Editor: U. VASUDEVA RAU, M.B., B.S.

'Grams: "ANTISEPTIC" P. O. Box 144 Phone: 22794

Subscription Rs. 15-00 Foreign Rs. 17-50 a year Single Copy Rs. 2-50 in advance

JAN RAZ-0012373

DX-00483-00004

EXHIBIT 65

IRCS Medical Science: Anatomy and Human Biology; Biochemistry; Clinical Biochemistry; Clinical Medicine; Clinical Pharmacology and Therapeutics; Developmental Biology and Medicine; Drug Metabolism and Toxicology; Metabolism and Nutrition; Nervous System; Psychology and Psychiatry; Social and Occupational Medicine. [*IRCS Med. Sci.*, 11, 1048-1049 (1983)]

Combined cholinergic precursor treatment and dihydroergotoxine mesylate in Alzheimer's disease

Nunzio Pomara, Robert Block, Joy Abraham, Edward F. Domino* and Samuel Gershon

*Lafayette Clinic and Wayne State University School of Medicine, 951 E. Lafayette, Detroit, Michigan 48207 and *Department of Pharmacology, University of Michigan, USA*

Paper received: 14th October, 1983; amended 2nd November, 1983

The consistent and selective reductions in the brain activity of choline acetyltransferase (1), the biosynthetic enzyme for acetylcholine, have led to numerous attempts at enhancing central cholinergic activity in individuals with Alzheimer's disease by means of cholinergic precursors (lecithin, choline) in the hope of ameliorating the cognitive dysfunctions in these patients. The outcome of these therapeutic strategies which have utilized cholinergic precursors alone has been generally disappointing (2). There is, however, a preliminary report from an open trial suggesting increased efficacy from the combination of choline with piracetam (3), a pharmacological agent which is thought to improve neuronal metabolism.

Dihydroergotoxine mesylate (Hydergine) is a widely prescribed agent for the treatment of elderly patients with dementia, which like piracetam is also thought to exert its beneficial effects by improving intraneuronal metabolism (4).

In the light of these considerations, we undertook the present double-blind study to assess psychometric effects of a combination of a cholinergic precursor (lecithin) and a 6 mg/day dose of Hydergine in individuals with Alzheimer's disease. A 6 mg/day dose of Hydergine was chosen because of recent reports (5) indicating that it is as safe as the 3 mg per day dose currently approved in the United States, and might possibly be more effective.

Patients and methods: Nine mild-to-moderately impaired individuals were recruited from the outpatient geriatric clinic for participation in this study. There were three females and six males (mean age 66.4; range 54—81). Subjects received medical, psychiatric, neuroradiological evaluations including a CAT scan, and routine laboratory investigations. All participants met the DSM III (6) criteria for Primary Degenerative Dementia (Alzheimer's disease). None of the subjects had been on any psychotropic medication.

Following a two-week placebo period, patients received oral tablets of Hydergine, 2 mg *t.i.d.* for 12 weeks. During the same period, they also received lecithin (95% phosphatidylcholine, purchased from the American Lecithin Company, Atlanta, Georgia) 10 gm *b.i.d.* for six weeks and placebo for six weeks in a double-blind crossover design.

At the end of the placebo period and at two week intervals thereafter, patients receiving psychometric testing consisting of Buschke's "Selective Reminding" test (7), digit span/supraspan, word fluency, and Sperling tasks (8), and three subtests of the Wechsler Memory Scale. Patients also filled out a Symptom Checklist and rated their memory on five questions from Squire's Memory Assessment. The psychiatrist made ratings on the Global Deterioration Scale (9).

Blood samples for determination of plasma and red blood cell (RBC) choline were also obtained at the same times. Choline levels were determined by a modification of the gas chromatographic method of Jenden and Hanin (10).

Plasma and RBC choline levels and selected psychometric measures in individuals with Alzheimer's disease receiving placebo, or Hydergine with placebo or Hydergine with lecithin (means ± SEM, n = 9)

	Placebo	Hydergine + Placebo (week 6)	Hydergine + Lecithin (week 6)
Choline (nmol/ml)			
Plasma***	18.3 ± 1.9	18.7 ± 2.4	38.5 ± 4.3 ‡
RBC	61.2 ± 24.2	42.4 ± 10.3	77.9 ± 15.7
Sperling test			
No. of letters	31.33 ± 3.10	35.44 ± 2.25†	33.56 ± 2.27
Buschke task-total recall			
No. of items	55.11 ± 4.71	49.44 ± 4.88†	55.44 ± 7.28
Squires Memory Assessment ratings			
Total over 5 questions	−2.67 ± 3.15	−0.78 ± 2.03	0.89 ± 2.32
Symptom Checklist rating			
"Trouble remembering things"**	2.56 ± 0.18	2.11 ± 0.20†	2.00 ± 0.17†
Global Deterioration Scale rating*	4.06 ± 0.21	3.78 ± 0.12	3.72 ± 0.19†

*Difference among three treatment conditions significant by one-way analysis of variance, P <: *0.05; **0.01; ***0.001. Difference from placebo significant by one-way analysis of variance, P <: †0.05; ‡0.01.*

Results: As indicated in the table, co-administration of lecithin and Hydergine increased plasma choline significantly relative to placebo alone. A similar but non-significant trend occurred for RBC choline. Co-administration of lecithin and Hydergine significantly increased both plasma ($P < 0.001$) and RBC ($P < 0.01$) choline relative to Hydergine alone.

Analyses of variance of the psychometric measures indicated no significant differences between Hydergine alone and the

Hydergine-lecithin combination. Hydergine-alone significantly improved performance on the Sperling Test, but there was no consistent pattern of improvement in response to either of the drug treatments on the other objective psychometric measures. On the other hand, both Hydergine alone and Hydergine plus lecithin, led to some significant improvements as compared to placebo in subjective psychometric measures. Patients' ratings on the Symptom Checklist item "trouble remembering things" showed significant subjective improvement after six weeks of Hydergine alone or Hydergine plus lecithin. Global Deterioration Scale ratings also improved, though only the contrast between placebo and Hydergine plus lecithin was significant.

Conclusions: As previously reported by others (5), we found the 6 mg/day dose of Hydergine to be quite safe. There were absolutely no adverse side effects associated with this treatment. Additionally, we found no increased toxicity during combined Hydergine-lecithin treatment. With respect to the effects on memory, we found no superiority of the Hydergine-lecithin combination over Hydergine alone. Both drug treatments led to some subjective improvement without any consistent improvements on objective psychometric measures as has been previously reported with Hydergine treatment (4, 5).

The discrepancy between our study and the improvements previously reported in response to the choline-piracetam combination in an open trial (3) may be due to the methodological differences between the studies, or it could possibly reflect significant differences between piracetam and Hydergine in their interactions with cholinergic precursors.

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EXHIBIT 66

Dated 30th November 1995

(1) Shire International Licensing B.V.

- and -

(2) Janssen Pharmaceutica N.V.

Global (excluding Japan)
Co-Development, Know-how and Supply Agreement
for Galanthamine

18959296

INDEX

18959296

THIS AGREEMENT is made the 30th day of November 1995

BETWEEN:-

(1) **Shire International Licensing BV** a company organised and existing under the laws of the Netherlands whose principal place of business is at Frederiksplein 42, 1017 XN, Amsterdam, the Netherlands ("Shire"); and

(2) **Janssen Pharmaceutica NV** a Belgian business corporation organised and existing under the laws of Belgium with its registered office at Turnhoutseweg 30, B-2340 Beerse, Belgium ("Janssen").

RECITALS

(A) By a licence agreement amended and restated on the same date as this Agreement between Synaptech and Shire Holdings Limited, Synaptech grants to Shire Holdings Limited an exclusive licence under the Patents and Synaptech Know-how to develop, make, have made, keep, use, market, sell and/or dispose of the Licensed Product throughout the Shire Territory and the United Kingdom and the Republic of Ireland.

(B) By an assignment made on the same date as this Agreement, Shire Holdings Limited assigned to Shire its rights and obligations under the above licence agreement in respect of the Shire Territory.

(C) By a sub-licence agreement made on the same date as this Agreement between Shire and Janssen, Shire grants to Janssen an exclusive sub-licence under the Patents and the Synaptech Know-how to develop, make, have made, keep, use, market, sell and/or dispose of the Licensed Product throughout the Shire Territory.

(D) By a licence agreement made on the same date as this Agreement between Synaptech and Janssen, Synaptech grants to Janssen an exclusive licence under the Patents and Synaptech Know-how to develop, make, have made, keep, use, market, sell and/or dispose of the Licensed Product throughout the Janssen Territory.

(E) Shire has entered into agreements in connection with the production of Natural Galanthamine and the development of a process for the production of Synthetic Galanthamine.

(F) Shire and Janssen wish to enter into this Agreement to cover various matters relating to the development manufacturing and supply of Galanthamine and Licensed Product including without limitation the following matters:-

(i) co-development of the Licensed Product within the Territory and the United Kingdom and the Republic of Ireland;

(ii) terms and conditions for the manufacture and supply of Galanthamine Raw Material and Finished Product;

(iii) the grant by Shire to Janssen of an exclusive licence to use Shire Know-how in the Territory;

(iv) the grant by Shire to Janssen of a semi-exclusive licence to use the Manufacturing Intellectual Property Rights and a non-exclusive licence to use the Chiroscience Intellectual Property Rights;

(v) the development of Galanthamine for the treatment of indications other than Alzheimer's disease and related dementias and the grant by Shire to Janssen of licences in respect of such indications; and

(vi) the co-promotion of the Licensed Product in the United Kingdom and the Republic of Ireland.

IT IS AGREED AS FOLLOWS:-

1. **Definitions**

In this Agreement the following words shall have the following meanings, unless the context requires otherwise:-

1.1	"Affiliate"	(1) any corporation or other business entity owning or directly or indirectly having effective control over the activities of a party to this Agreement or (2) any corporation or other business entity that is directly or indirectly controlled by a party to this Agreement or (3) any corporation or other business entity that is directly or indirectly controlled by any corporation or business entity that directly or indirectly has effective control of a party to this Agreement;
1.2	"Average Cost of Galanthamine Raw Material"	the cost as defined in Clause 6.1.8;
1.3	"Business Partner"	a third party that is (1) Janssen's principal distributor in a country of the Territory where Janssen does not have an Affiliate responsible for the marketing and selling of Janssen products; or (2) a sublicensee appointed by Janssen pursuant to Clause 2.4 of the Synaptech-Janssen Licence Agreement;
1.4	"CFS"	Chronic Fatigue Syndrome;
1.5	"Chiroscience"	Chiroscience Limited a company registered in England under company registration number 2667953 whose registered office is at No. 283 Cambridge Science Park, Milton Road, Cambridge, SB4 4WE;
1.6	"Chiroscience Agreement"	The agreement dated 19th April 1995 between Chiroscience and Shire International Licensing BV;

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18959296

1.7	"Chiroscience Intellectual Property Rights"	all Intellectual Property Rights existing as at 25th October 1994 developed by Chiroscience and/or owned by Chiroscience and/or licensed to Chiroscience upon terms whereby such rights may be used by Chiroscience in or in connection with the research to be conducted under the Chiroscience Agreement;
1.8	"Chiroscience Process"	the process for the manufacture of Synthetic Galanthamine as developed by Chiroscience;
1.9	"Ciba Data"	the full and complete data and related summaries and documentation generated by the Ciba Geigy study MIN Number 921003 Rat 26/52 week and study MIN Number 921004 Dog 26/52 week;
..10	"Co-Development Plan"	the plan directed to the development of the Licensed Product as set out in Schedule 3 and as updated from time to time by the DMC pursuant to Clause 4.6.5;
1.11	"Commercial Delivery"	the first sale to a Customer for commercial use of any Licensed Product in a country of the Territory after the grant of Product Approval in that country;
1.12	"Concluded Shire Data"	the data from studies completed prior to the date of this Agreement by or on behalf of Shire as described in Schedule 4;
1.13	"Customers"	any third party, other than an Affiliate or Business Partner of Janssen, to whom Janssen, its Affiliates or Business Partners supply the Licensed Product;
14	"Data Exclusivity"	this expression shall include without limitation the exclusivity referred to in Article 4.8 of Directive 65/65/EEC as amended by Directive 87/21/EEC and any other rule of law in any country of the Territory whereby a third party is prevented from relying on, or referring to, data filed in support of the Product Approvals in order to obtain regulatory approval for its own product provided that for purposes of this Agreement the period of Data Exclusivity in respect of any country shall be deemed to extend for a maximum period of 10 years from the date of final grant of Product Approval in such country.

1.15	"Development Cost Plan"	the cost plan set out in Schedule 5 containing the estimated cost of developing the Licensed Product as the same may be revised each year pursuant to Clause 4.6.6;
1.16	"Development Data"	all data, raw data, charts, studies, summaries, analyses, reports and other information relating to the Licensed Product generated by or on behalf of the parties before, on, or after the date of this Agreement (including without limitation the Concluded Shire Data) other than data, know-how or other information relating to the manufacture and/or production of Galanthamine;
1.17	"DMC"	the Development Management Committee which shall be appointed and shall operate in accordance with the provisions of Clause 4;
1.18	"Excluded Territory"	the United Kingdom and the Republic of Ireland and any countries for which Shire acquires the exclusive rights pursuant to the buy back options set out in Clauses 19 and 20 and any countries for which Janssen's rights are cancelled pursuant to Clause 25;
1.19	"Finished Product"	any finished pharmaceutical formulation of the Licensed Product suitable for administration to patients;
1.20	"Galanthamine"	galanthamine or pharmaceutically acceptable acid addition salts thereof;
1.21	"Galanthamine Raw Material"	Galanthamine of suitable purity and in an appropriate form for converting into Finished Product. For the avoidance of doubt Galanthamine Raw Material shall include Natural Galanthamine and/or Synthetic Galanthamine as the context may require;
1.22	"Improvements"	any new technique or formulation or any new application of an old technique that is relevant to the use of Galanthamine for the treatment of Alzheimer's disease and/or related dementias and having application or potential application to the Licensed Product. For the avoidance of doubt Improvements excludes Development Data and Manufacturing Improvements;

LP
18959296

1.23	"International Registration File"	the international registration file for the Licensed Product compiled by Janssen (i) so as to satisfy the requirements of an NDA in the United States (ii) so as to satisfy the requirements of the Notice to Applicants for marketing authorisation for Proprietary Medicinal Products for human use in the European Union and (iii) in a form which can be submitted as such to national health authorities in any other country or be used as a basis for a national application for marketing authorisation for Licensed Products in the specific format required by such national health authorities;
1.24	"Janssen Territory"	the United States of America, Canada, Mexico, the Republic of Korea, Taiwan, Thailand and Singapore;
1.25	"Licensed Product(s)"	any product containing Galanthamine (whether Natural Galanthamine and/or Synthetic Galanthamine) which is used for, and/or intended to be used for, the treatment of Alzheimer's disease and/or related dementias in the Territory;
1.26	"Major Countries"	the countries listed in Schedule 9;
1.27	"Manufacturing Improvements"	any improvements relating to or useful in the manufacture or production of Synthetic Galanthamine;
1.28	"Manufacturing Intellectual Property Rights"	(1) any patents and/or patent applications; and (2) all proprietary information including but not limited to inventions, practices, methods, knowledge, know-how, whether or not patented, owned by Shire or with respect to which Shire has the ability to grant a license or sublicense in accordance with the terms of this Agreement without breaching any agreement with a third party in connection with such intellectual property right and which patents, patent applications and proprietary information relate to the synthesis and manufacture of Synthetic Galanthamine;
1.29	"Manufacturing Patents"	any patents forming part of the Manufacturing Intellectual Property Rights;
1.30	"Natural Galanthamine"	Galanthamine extracted from plant bulbs as referred to in Clause 16;

1.31	"NDA"	NDA shall mean a New Drug Application and supplements filed pursuant to the requirements of t FDA, including all documents, data and oth information concerning the Licensed Product whi are necessary for, or included in, FDA approval market the Licensed Product in the United States America as more fully defined in 21. C.F.R. §314.5 seq;
1.32	"Net Sales Value"	the amount billed or invoiced by Janssen, its Affiliat or Business Partners to Customers for sales Licensed Product in the Territory less freight, sal taxes, trade or ordinary discounts, governme rebates and amounts repaid or credited because return of goods;
1.33	"Patents"	the patents identified in the attached Schedule 1 a any extensions of such patents and under whic Janssen is granted an exclusive licence in t Synaptech-Janssen Licence Agreement or exclusive sub-licence under the Shire-Janssen Sul licence Agreement. The Patents shall be deemed n to extend to any analogues of Galanthamine that m be specified in any patent listed in Schedule 1;
1.34	"Primary Royalty Rate"	the Primary Royalty Rates as specified in Clau 6.1.7;
1.35	"Product Approval"	the grant of all necessary governmental and regulato approvals to sell the Licensed Product in any count of the Territory including without limitatic acceptable pricing and reimbursements;
1.36	"Quarter"	the quarter periods ending, around March, Jun September and December;
1.37	"Secondary Royalty Rate"	the Secondary Royalty Rates as specified in Clau 6.1.7;
1.38	"Shire-Janssen Sub-licence Agreement"	the sub-licence agreement made the same date as th Agreement between Shire and Janssen in which Shi grants to Janssen an exclusive sub-licence under t Patents and the Synaptech Know-how in the Shi Territory in connection with the use of Galanthami in the treatment of Alzheimer's disease and/or relat dementias;

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1.39	"Shire Know-how"	all information (other than Synaptech Know-how and the Manufacturing Intellectual Property Rights) from time to time during this Agreement in Shire's possession or under its control and which it is free to disclose relating to the use of Galanthamine in the treatment of Alzheimer's disease and related dementias;
1.40	"Shire Territory"	the entire world with the exception of the United Kingdom, the Republic of Ireland, the Janssen Territory and Japan;
1.41	"Standard Cost	the actual cost of production (excluding VAT and other sales taxes and duties, freight charges, insurance charges and freight-packaging charges). Such cost to include (1) the direct costs of production (such as raw materials, labour, product packaging and quality control testing); (2) any licence fees payable to third parties in respect of such production and (3) such overhead costs and capital depreciation costs as are fairly and reasonably attributable to such production in accordance with the producers general accounting policy for the same or similar types of production.
1.42	"Study GAL 93-01"	the phase II dose optimisation study described in Schedule 6;
1.43	"Study GAL 95-05"	the phase III study described in Schedule 7;
1.44	"Synaptech"	Synaptech Inc. a corporation organised and existing under the laws of the State of New York;
1.45	"Synaptech Analogues"	analogues of Galanthamine claimed by any of the Patents or in any granted patents which are (1) owned by Synaptech, its Affiliates and/or Dr Bonnie Davis and (2) were filed before the date of this Agreement or claim priority from an application filed before the date of this Agreement;
1.46	"Synaptech-Janssen Licence Agreement"	the licence agreement made the same date as this Agreement between Synaptech and Janssen in which Synaptech grants to Janssen an exclusive licence under the Patents and the Synaptech Know-how in the Janssen Territory in connection with the use of Galanthamine in the treatment of Alzheimer's disease and related dementias;

1.47	"Synaptech-Shire Licence Agreement"	the licence agreement amended and restated on the same date as this Agreement, between Synaptech and Shire Holdings Limited;
1.48	"Synthetic Galanthamine"	Galanthamine produced using a synthetic process;
1.49	"Synaptech Know-how"	information supplied to Janssen by Synaptech under the provisions of the Synaptech - Janssen Licence Agreement and information supplied to Shire by Synaptech under the provisions of the Synaptech-Shire Licence Agreement;
1.50	"Territory"	the Shire Territory and the Janssen Territory;
1.51	"Tertiary Royalty Rate"	the Tertiary Royalty Rates as specified in Clause 6.1.7;
1.52	"Trade Marks"	the trade marks selected by Janssen pursuant to Clauses 11.1 and 11.2 and any trade mark registrations or applications therefor in the name of Janssen or its Affiliates or in the name of Shire or its Affiliates in the United Kingdom and the Republic of Ireland.

2. Grant Of Licence

2.1 Know-how and Manufacturing Licence

2.1.1 In support of the licences granted under the Synaptech-Janssen Licence Agreement and the Shire-Janssen Sub-licence Agreement Shire shall grant to Janssen:

2.1.1.1 an exclusive licence under the Shire Know-how to develop, make, have made, use, keep, sell and/or dispose of the Licensed Product in the Territory;

2.1.1.2 (subject to Clauses 2.1.3 and 2.1.4) an exclusive licence to use the Manufacturing Intellectual Property Rights for the manufacture of Synthetic Galanthamine in the Territory and the United Kingdom and the Republic of Ireland solely for use in Licensed Products supplied by Janssen, its Affiliates and/or Business Partners and for supply to Shire pursuant to Clause 16.3.1; and

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2.1.1.3 a non-exclusive sub-licence to use such part(s) of the Chiroscience Intellectual Property Rights as may reasonably be required for the use and exploitation of the Manufacturing Intellectual Property Rights for the manufacture of Synthetic Galanthamine in the Territory and the United Kingdom and the Republic of Ireland solely for use in Licensed Products supplied by Janssen, its Affiliates and/or Business Partners and for supply to Shire pursuant to Clause 16.3.1.

2.1.2 Janssen shall be entitled to exercise its rights under this Clause 2.1 through its Affiliates and Business Partners provided that Janssen shall:

2.1.2.1 remain solely responsible and be the guarantor of the performance by its Affiliates and Business Partners; and

2.1.2.2 procure that its Affiliates and Business Partners comply fully with the provisions of this Agreement.

2.1.3 Shire shall retain the right to have manufactured on its behalf Synthetic Galanthamine worldwide for use (1) in the Excluded Territory and (2) worldwide for improvements in benzodiazepine treatment and the treatment of mania subject to the approval of Janssen pursuant to Clause 18.4.

2.1.4 To the extent that the licence granted in Clause 2.1.1.2 relates to intellectual property rights owned and/or developed by Chiroscience then the grant of such licence shall be subject to satisfactory renegotiation of the Chiroscience Agreement pursuant to Clause 16.4.

2.2 Limit of Grant

Janssen shall have no right or licence under the Shire Know-how, the Manufacturing Intellectual Property Rights or the Chiroscience Intellectual Property Rights except as is expressly granted in this Clause 2.

3. Initial And Milestone Payments

3.1 Initial Payment

3.1.1 Janssen shall pay to Shire in full without any deductions whatsoever the following non-refundable payments:-

3.1.1.1 £1,000,000 (sterling) in consideration of the grant of the rights and licences under this Agreement;

3.1.1.2 £1,900,000 (sterling) in consideration of Study GAL 93-01 having met the success criteria agreed by the parties prior to the date of this Agreement; and

3.1.1.3 £2,501,850 (sterling) representing 97.5% of the costs incurred by Shire and its Affiliates in developing the Licensed Product prior to 30th September 1995 as set out in the Development Cost Plan.

3.1.2 The above payments shall be due on the date of this Agreement and shall be paid within 7 days of the date of this Agreement.

3.2 Milestone Payments

Janssen shall pay to Shire in full without any deductions whatsoever the following non-refundable sums:-

3.2.1 £550,000 (sterling) within 30 days of the submission of the NDA in the United States of America;

3.2.2 £550,000 (sterling) within 30 days of the submission of the first application for Product Approval in any Major Country other than the United States of America;

3.2.3 £670,000 (sterling) within 30 days of the grant of NDA in the United States of America; and

3.2.4 £670,000 (sterling) within 30 days of the grant of the first Product Approval in any Major Country other than the United States of America.

3.3 Share Purchase Agreement

Janssen and Shire respectively shall procure that the Johnson & Johnson Development Corporation and Shire Pharmaceuticals Group Plc execute a Share Purchase Agreement on fair and reasonable terms to reflect the points set out in Schedule 10 as soon as practicable.

3.4 Payment under other Agreements

For the avoidance of doubt the payments due under this Agreement shall be payable in addition to the payments due under the Shire-Janssen Sub-licence and the Synaptech-Janssen Licence Agreement.

4. Co-Development Programme & Product Approvals

4.1 Janssen and Shire shall undertake the co-development of the Licensed Product in accordance with the Co-Development Plan and at the direction of the DMC.

4.2 The DMC shall consist of the representatives from both parties who are responsible for the activities to be conducted under the Co-Development Plan. To ensure the flexibility of the DMC, the representatives as well as the number of representatives in the DMC may change in accordance with the requirements of the different stages of the Co-Development Plan. Regardless of the number of representatives from each party in the DMC, each party shall have one vote.

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4.3 The DMC shall meet quarterly alternately at each other's offices or on such other occasions as may be reasonably requested by either party throughout each stage of the co-development of the Licensed Product. The parties shall pay their own costs in attending such meetings.

4.4 All decisions of the DMC shall be made unanimously. If the DMC is unable to reach unanimous agreement upon any material matter (having used all reasonable endeavours and negotiated in good faith) within 30 days then subject to Clause 4.5 Shire shall have the final decision in the case of disputes concerning Chiroscience and third-party suppliers of the Galanthamine Raw Material (including without limitation MacFarlan Smith) and when to file for Product Approval in the Excluded Territory (except when a country within the Excluded Territory is used as the EC Rapporteur Country for EC Product Approval) and when to make the transition to the use of Synthetic Galanthamine in the Excluded Territory and Janssen shall have the final decision in all other cases including without limitation all technical decisions relating to the development and upscaling of Janssen's Synthetic Galanthamine process and also decisions as to when to make the transition to the use of Synthetic Galanthamine in the Territory.

4.5 If either party reasonably believes that any final decision of the other party pursuant to Clause 4.4 would seriously delay or prejudice grant of Product Approval in any Major Country or would seriously jeopardise the supply of an adequate quantity of Galanthamine at an acceptable price then such party may refer the matter to an expert for resolution pursuant to Clause 28.13. In making any decision, such expert shall in addition to other factors take into account the competitive market position as described in Clause 9.2.3..

4.6 The DMC shall be responsible for the day to day management and conduct of all aspects of the co-development of the Licensed Product and shall (in particular, but without limitation):-

4.6.1 define the detailed objectives and each relevant phase of work to be undertaken in each phase of the co-development;

4.6.2 design and agree the work programs for each phase of the co-development;

4.6.3 assess whether objectives have been met in respect of each phase of the co-development;

4.6.4 report to the management of each of the parties regularly upon the progress of the co-development;

4.6.5 make revisions to the timetable set out in the Co-Development Plan provided that any extensions to the timetable shall be limited to the minimum necessary and any decision to extend the timetable shall be subject to the provisions of Clause 4.5 above; and

4.6.6 propose on an annual basis revisions to the Development Cost Plan for submission to the parties provided that no revisions shall be made to the Development Cost Plan which exceed the limits set out in Clause 5.4 without the prior written approval of both parties.

4.7 All Product Approvals shall be applied for in Janssen's name and if granted held in Janssen' name, other than the Product Approvals for the Excluded Territory which shall be applied fc in Shire's name and if granted held in Shire's name.

4.8 Janssen shall be responsible for applying for, pursuing and maintaining Product Approval and other regulatory approvals relating to the Licensed Products and/or their production i the Territory

4.9 Shire shall be responsible for applying for, pursuing and maintaining Product Approvals an other regulatory approvals relating to the Licensed Products and/or their production in th United Kingdom and the Republic of Ireland.

4.10 Each party shall, free of charge, promptly provide the other party with such assistance as th other party may reasonably request in connection with its obligations under Clause 4.8 or 4.' above including without limitation providing Development Data, the Internationa Registration File and/or other information relating to the Licensed Product and preparing a necessary documentation required (such as certificates and other administrative documents for reference in the application for Product Approval.

5. Development Costs

5.1 Costs incurred by the parties after 30th September 1995 in developing the Licensed Produc according to the Co-Development Plan shall be divided between the parties in the followin proportions:-

5.1.1.1 Janssen 97.5%; and

5.1.1.2 Shire 2.5%.

5.2 The costs division shall be calculated on a monthly basis and invoices shall be raised b Janssen or Shire (as appropriate) in accordance with the above proportions and shall b settled by Janssen or Shire (as appropriate) within 30 days of receipt of such invoice.

5.3 The development costs for the period after 30th September 1995 as set out in th Development Cost Plan are estimates only. For the purposes of this Agreement and i particular Clause 5.1 the actual cost of each item of development work set out in the Cc Development Plan shall be as follows:-

5.3.1 In the case of items of development work carried out by third parties (other tha Affiliates of the parties) the cost shall be the amount actually invoiced by the thir party concerned to the party responsible for that development work plus any VA or any sales tax or duty payable in respect thereof.

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5.3.2 In the case of items of development work carried out by the parties and/or their Affiliates, the cost shall be the reasonable direct and indirect cost of such development work provided that such cost shall not exceed the costs set out in the Development Cost Plan for such item of development work by more than 10%. Direct overheads shall be allocated to the development work in accordance with the usual practice of the party carrying out the item of development work concerned. Each party shall have the right to appoint an independent auditor to inspect the other parties records and books of account (and those of its Affiliates) for the purpose of verifying the costs concerned and the allocation of overheads. Any dispute as to what the reasonable direct and indirect cost of items of development work should be, shall be referred to an arbitrator pursuant to Clause 28.12.

5.4 The provisions of this Clause 5 shall apply to any costs incurred in developing the Licensed Product up to a maximum of 110% of the total estimated development costs specified in the then current Development Cost Plan. Any costs in excess of 110% of the total estimated development costs specified in the then current Development Cost Plan shall require the DMC to submit a new plan to Shire and Janssen for written approval.

5.5 Janssen shall give Shire 30 days notice of its intention to give notice under Clauses 4.3 or 4.4 of the Synaptech-Janssen Licence Agreement stating whether or not Janssen intends to purchase the right to use the Ciba Data. If Janssen notifies Synaptech pursuant to Clause 4.3 of the Synaptech-Janssen Licence Agreement that Janssen requires the Ciba Data and Janssen pays the purchase price for the Ciba Data pursuant to Clause 4.5.1 of the Synaptech-Janssen Licence Agreement and Clause 4.3.1 of the Shire-Janssen Sub-licence Agreement then the purchase price of the Ciba Data as paid by Janssen to Synaptech and Shire shall be divided between the parties in the proportions 97.5% to Janssen and 2.5% to Shire.

5.6 Any payments received by the parties in respect of the use of the Ciba Data in Japan shall be divided between the parties in the proportion 97.5% to Janssen and 2.5% to Shire. If the purchase price for the Ciba Data attributable to Japan shall be recovered by Janssen making deductions from sums otherwise payable to Synaptech then at the times such deductions are made Janssen shall pay to Shire 2.5% of the value of such deductions.

5.7 Janssen shall reimburse Shire for 97.5% of the £80,000 annual consultancy fee payable by Shire to Dr Bonnie Davis within 30 days of receipt by Janssen of evidence of payment of the consultancy fee to Synaptech. Janssen's obligation under this Clause shall continue for either 5 years from the date of this Agreement or until the grant of NDA approval for the Licensed Product by the FDA in the United States of America, whichever occurs earlier.

5.8 Janssen shall have the right within 14 days of the date of this Agreement to send a representative to Shire to audit the development costs incurred by Shire in relation to the Licensed Product up to 30th September 1995 as set out in the Development Cost Plan. Shire shall afford Janssen's representative all reasonable access to Shire's documents and records of account solely for the purposes of conducting the audit.

5.9 If Janssen's representative concludes that there is a discrepancy of more than 2.5% between the £2,566,000 total set out in the Development Cost Plan and the total evident from the audit then:-

5.9.1 the parties shall promptly meet to establish how the discrepancy arose and agree the amount of any discrepancy;

5.9.2 if agreement is reached pursuant to Clause 5.9.1 above then a consequential adjustment shall be made in the next cost division between the parties pursuant to Clause 5.2; and

5.9.3 if agreement cannot be reached pursuant to Clause 5.9.1 then either party may refer the matter to an expert for resolution pursuant to Clause 28.13.

6. ROYALTIES

In consideration for the grant of the licences set out in Clause 2 and for the other benefits accruing to Janssen under this Agreement, Janssen shall pay to Shire the royalties set out in Clause 6.1. For the avoidance of doubt the payments and royalties due under this Agreement shall be payable in addition to payments made under the Shire-Janssen Sub-licence Agreement and the Synaptech-Janssen Licence Agreement.

6.1 Amount of Royalty

6.1.1 Janssen shall pay to Shire, subject to Clause 6.1.4, the Primary Royalty Rate on the Net Sales Value of all Licensed Product sold by Janssen, its Affiliates or Business Partners in any country of the Territory where a Patent remains in force and/or Data Exclusivity applies in such country.

6.1.2 Janssen shall pay to Shire, subject to Clause 6.1.5, the Secondary Royalty Rate on the Net Sales Value of all Licensed Product sold by Janssen, its Affiliates or Business Partners in any country of the Territory where a Patent has ceased to be in force and Data Exclusivity has ceased to apply. Such royalty shall be payable for a period of ten years following whichever is the later of (1) the date upon which the last Patent ceased to be in force in such country or (2) the date upon which Data Exclusivity ceased to apply in such country.

6.1.3 Janssen shall pay to Shire, subject to Clause 6.1.5, the Secondary Royalty Rate on the Net Sales Value of all Licensed Product sold by Janssen its Affiliates or Business Partners in any country of the Territory where at the date of this Agreement there is no Patent in force and Data Exclusivity does not apply. Such royalty shall be payable for a period of ten years from the date of the first Commercial Delivery of Licensed Product in such country.